



TITLE:

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## SHORT COMMUNICATION

### Disseminated *Mycobacterium mantenii* Infection with Multiple Purulent Cutaneous Lesions

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Non-tuberculous mycobacteria (NTM) can affect a range of organs, leading to various clinical manifestations, including lymphadenitis, dermatitis, and skeletal infection (1). In immunocompromised patients, NTM sometimes spread systemically via bacteraemia and may lead to fatal conditions, termed disseminated NTM infections (2). *Mycobacterium mantenii*, which is a slow-growing mycobacteria, has been isolated, but its pathogenicity is largely unknown (3).

Tocilizumab is an interleukin (IL)-6 receptor monoclonal antibody that inhibits signalling of IL-6, which plays a pivotal role in the pathogenesis of diseases such as rheumatoid arthritis and Castleman's disease (4, 5).

We report here a case of disseminated *M. mantenii* infection that emerged during treatment for Castleman's disease, and was substantially aggravated by administration of prednisolone and tocilizumab.

## CASE REPORT

A 70-year-old man was referred to our department for the evaluation of facial pustules and multiple subcutaneous nodules all over his body. The patient had a history of NTM infection; small lung nodules had been found 7 years previously, and mycobacterium culture from sputum was positive for *M. scrofulaceum* and *M. paraffinicum*. Since then, because the patient had been asymptomatic, he had been followed without medication.

Three years later, the patient's cervical and axillary lymph nodes became swollen and leg oedema developed. He had no fever, but his serum C-reactive protein (CRP) level increased to 14.3 mg/dl (normal <0.2 mg/dl). Computed tomography with fluorodeoxyglucose positron emission tomography (FDG-PET) revealed enlargement of multiple lymph nodes with increased accumulation of 18F-FDG. A biopsy of cervical lymph nodes revealed granulation tissue with inflammation and fibrosis, but was negative for Zeel-Nielsen stain and mycobacterium culture. Lymph node findings were not pathologically specific for Castleman's disease, but based on the clinical findings and greatly elevated serum IL-6 level of 105 pg/ml (normal <4.0 pg/ml), the patient was diagnosed with Castleman's disease. Prednisolone was administered orally at a dose of 0.5 mg/kg/day.

After treatment, the patient remained in a good clinical condition for approximately 3 years during prednisolone tapering, but oedema of the extremities and multiple reddish nodules with pruritus emerged on his face 6 months prior to this consultation, which spread to his trunk and extremities. Because Zeel-Nielsen staining of the nodules was negative for mycobacterium, they were considered to be an exacerbation of Castleman's disease. In addition to oral prednisolone, 0.125 mg/kg/day, systemic tacrolimus, 1.5 mg/day/kg, was administered, but discontinued after 2 weeks because the facial papules enlarged and increased

in number. Therefore intravenous tocilizumab, 480 mg/m<sup>2</sup>, every 2 weeks was added 3 months prior to this consultation. Subsequently, facial nodules formed pustules, which disintegrated into ulcerated lesions. The patient was referred to our department because of prominent aggravation of cutaneous manifestations.

Physical examination revealed that multiple pustules aggregated on the cheeks and nose, and some of them were ulcerated (Fig. 1a and b). In addition, red papules and pustules were observed on the central area of the chest (Fig. 1c). Well-circumscribed, elastic-soft, asymptomatic subcutaneous nodules were present on the back and limbs.

Skin biopsy was performed on the facial pustules, and histology revealed that inflammatory cells, including lymphocytes, neutrophils, and plasma cells, infiltrated markedly, with oedematous changes in the stromal tissue (Fig. 2). Increased capillary, epithelioid and multinucleated giant cells, forming non-necrotizing granulomas, were noted (Fig. 2a and b). Many acid-fast bacilli were visible with Zeel-Nielsen staining (Fig. 2c), and *M. mantenii* was identified in mycobacterium culture. The patient subsequently presented with multiple nodules in the pharynx and paranasal sinuses, which eventually tested positive for mycobacterium by culture.

NTM were also detected in culture of the lung, pharynx, and skin, and the patient was diagnosed as having a disseminated NTM infection during treatment for Castleman's disease. Tocilizumab was discontinued and prednisolone was decreased gradually to 0.2 mg/kg/day. Treatment with levofloxacin, rifampicin, ethambutol, and amikacin was administered. The pustules and erythematous papules disappeared and superficial ulcers with peripheral epithelization formed in approximately 2 months.



Fig. 1. (a, b) Numerous aggregated ulcerated pustules on the cheeks and nose. (c) Erythematous papules and pustules on the central area of the chest.

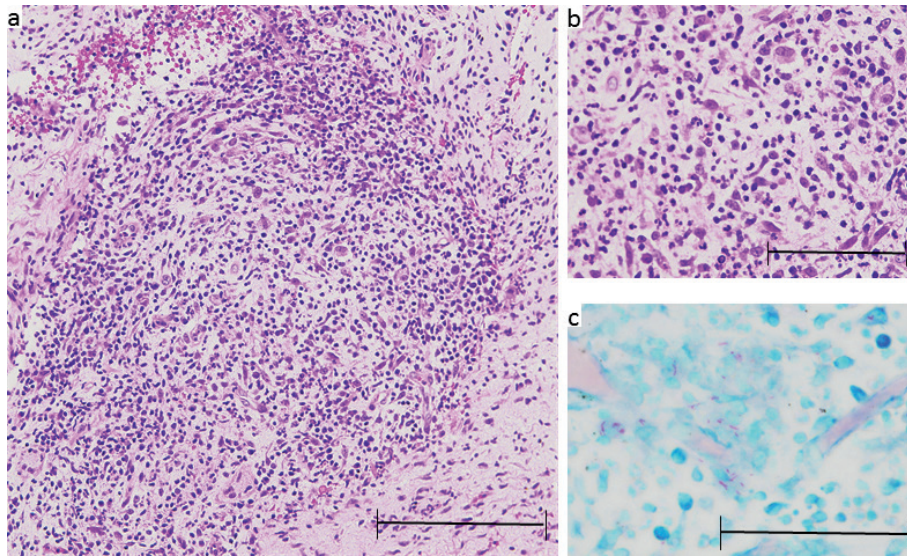


Fig. 2. Pathological findings of facial pustules. (a) Formation of non-necrotizing granulomas. Scale bar: 100  $\mu$ m. (b) Marked infiltration of inflammatory cells, consisting of plasma cells, neutrophils, lymphocytes, and histiocytes. Scale bar: 50  $\mu$ m. (c) Zeel-Nielsen staining. Scale bar: 50  $\mu$ m.

## DISCUSSION

Patients with disseminated NTM infections are frequently immunocompromised, e.g. individuals with acquired immune deficiency syndrome. In addition to the importance of interferon (IFN)- $\gamma$ , IL-12, and tumor necrosis factor (TNF)- $\alpha$  in host defence against NTM infection, IL-17-producing T helper cells (Th17) cells have been reported to play an essential role in NTM infection-immunity (6). IL-6 promotes preferential differentiation of Th17 in the condition of transforming growth factor (TGF)- $\beta$  (7). Tocilizumab reduces IL-6 pleiotropic actions on T-cell activation, antibody secretion and Th17 differentiation, which may have contributed to aggravation of the clinical manifestations of the skin lesions in this case (7).

The clinical appearance of skin lesions caused by NTM is diverse, and includes solitary nodules, ulcers, furuncles and abscesses (8). This patient had an accumulation of pustules and red papules in seborrhoeic areas, as well as multiple subcutaneous nodules in which *M. mantenii* was detected. *M. mantenii* is a slow-growing, scotochromogenic mycobacteria, which was first isolated from 2 patients with chronic bronchitis in 2009 (3). *M. mantenii* is most closely related to *M. scrofulaceum* from the perspective of genetic, phenotypic and clinical data (3). Various kinds of NTM species are known to cause cutaneous diseases, but no reports have been found on *M. mantenii* as a cause of skin infection. *M. scrofulaceum* is rare cause of cutaneous infections (9), but disseminated *M. scrofulaceum* infections with multiple skin ulcers and abscesses have been reported in immunocompromised patients (10). Given that *M. mantenii* is similar to *M. scrofulaceum*, it can be assumed that *M. mantenii* might have spread hematogenously and formed multiple pustules and subcutaneous nodules in immunosuppressive conditions caused by the administration of tocilizumab

and long-term use of prednisolone. To our knowledge, this is the first report of skin lesions that may have been induced by infection with *M. mantenii*.

The authors declare no conflicts of interest.

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